PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH2004/000147	12.03.2004	

International Patent Classification (IPC) or both national classification and IPC
C07D217/14, C07D217/16, C07D401/04, C07D233/16, A61K31/472, A61K31/4725, A61P35/00

Applicant
ANALYTECON S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

vanVoorsttotVoorst,M

Telephone No. +49 89 2399-8280

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18,19

because:

☒ the said international application, or the said claims Nos. 18,19 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17,20-22
	No:	Claims	

2. Citations and explanations

see separate sheet

AD SECTION III:

1. For the assessment of the present claims 18 and 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

   Claims 18 and 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

AD SECTION V:

1. The following documents are considered in this communication:

   D1: US-B-6 337 3381 (KOZLOWSKI MICHAEL R ET AL) 8 January 2002 (2002-01-08)
   D2: WO 03/048133 A (BARLAAM BERNARD ; PAPE ANDREW (GB); THOMAS ANDREW (GB); ASTRAZENECA AB) 12 June 2003 (2003-06-12)
   D3: EP-A-1 113 007 (PFIZER) 4 July 2001 (2001-07-04)
   D4: LEE, JI SUN ET AL: "Synthesis of 1,2,3,4-tetrahydroisoquinoline-2-sulfonic acids" BULLETIN OF THE KOREAN CHEMICAL SOCIETY , 24(7), 1041-1044 CODEN: BKCSDE; ISSN: 0253-2964, 2003, XP002304792

2. Although a certain overlap exists between the compounds of general formula (I) disclosed in D3 and the present compounds, the subject-matter claimed is considered to represent a novel selection, whereby the new technical feature resides in the specific substitution of the isoquinoline moiety.
   None of the other prior art documents cited in the International Search Report disclose the compounds claimed, but refer to heteroaryl-aryl ureas (D1), 2,4-(subst)aminopyrimidines (D2) and 1,2,3,4-tetrahydroisoquinoline-2-sulfonic acids (D4).
   Having regard to the above, the subject-matter according to claims 1-22 appears

to meet the requirements of Article 33(2) PCT.

3. Closest prior art comprises the compounds disclosed in D1 and D2, which possess similar pharmacological properties as the present compounds, and those disclosed in D3 (estrogen agonists/antagonists) and D4 (no activity disclosed), which are structurally closely related to the present compounds, cf Example 64 in D3 and compound 9o in D4.
The problem to be solved was to provide compounds capable of down-regulating or inhibiting the expression or function of the insulin-like growth factor-1 receptor, which are thus useful in the prevention or treatment of cancer and other abnormal cell growth.
Having regard to both the structural and pharmacological profile of the prior art compounds it is considered that the skilled person faced with this problem would not have expected this activity from the compounds claimed as demonstrated by the Applicant on pages 40-44 of the description.
Therefore the subject-matter according to claims 1-22 appears to comply with the requirements of Article 33(3) PCT.

4. No objections with regard to Article 33(4) PCT arise for claims 1-17 and 20-22, however, see Section III above.